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(21) International Application Number: PCT/US98/27619 (22) International Filing Date: 23 December 1998 (23.12.98) (30) Priority Data: 09/000,673 30 December 1997 (30.12.97) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventors: KULKARNI, Prakash, Shriram; 13 Lord Sterling Drive, Parsippany, NJ 07054 (US). SHAH, Bharat, Bogilal; 655 Linden Avenue, Ridgefield, NJ 07657 (US). MAITRA, Amitava; 28 Rodio Court, Sayreville, NJ 08872 (US). DE VITO, Joseph, Michael; 49 Acorn Avenue, Middletown, NY 10941 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING BUPROPION HYDROCHLORIDE AND AN INORGANIC ACID STABILIZER (57) Abstract Novel, stable formulations of bupropion hydrochloride are provided which will maintain at least 80% of initial bupropion hydrochloride potency after one year. Methods of inhibiting degradation of bupropion hydrochloride are also provided.		

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**PHARMACEUTICAL COMPOSITION CONTAINING BUPROPION
HYDROCHLORIDE AND AN INORGANIC ACID STABILIZER**

Background of the Invention

5

Bupropion hydrochloride is a common antidepressant sold in immediate release, modified release, and extended release tablet forms. See U.S. Patent Nos. 3,819,706 and 3,885,046. As with many pharmaceuticals, the stability of bupropion hydrochloride is affected by a number of factors including formulation
10 microenvironments and storage conditions.

One formulation of bupropion hydrochloride is taught by Ruff et al., U.S. Patent No. 5,358,970 to prevent or inhibit degradation of bupropion hydrochloride using one of the stabilizers L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulfite, citric acid, tartaric acid and L-cystine dihydrochloride.
15

Description of the Invention

In accordance with the present invention is provided a novel pharmaceutical composition comprising bupropion hydrochloride and a pharmaceutically acceptable
20 stabilizer.

Bupropion hydrochloride is disclosed in the aforementioned patents as well as in the *Merck Index*, Twelfth Edition, entry no. 1523.

Stabilizer, as the term is used herein, means a compound which inhibits or prevents the degradation of bupropion hydrochloride so that it can be used in a
25 pharmaceutical formulation while retaining much of its potency. Stabilizers useful in accordance with the present invention retain at least about 80% of the potency of bupropion hydrochloride and preferably at least 90% of potency after one year of storage at room temperature (59-77°C) at 35-60% humidity. When used herein the term "potency" means the weight of bupropion hydrochloride remaining in a
30 formulation after a period of time has elapsed, for example about a year under ambient conditions or about 12 weeks at about 40°C and about 75% relative humidity, expressed as a percentage of the initial weight of bupropion hydrochloride in that formulation. The weight is measured by suitable quantitative analytical techniques such as HPLC. Thus, a tablet containing 100 mg of bupropion hydrochloride should retain
35 at least 80 mg and preferably more than 90 mg of bupropion hydrochloride at the end of 1 year in the presence of stabilizers of the present invention.

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Suitable stabilizers of the present invention are inorganic acids which at a concentration of about 0.31% w/w form an aqueous solution having a pH of from about 0.5 to about 4.0.

5 The stability of the formulation was tested in accordance with industry standards by storage for four to twelve weeks at about 40°C and about 75% relative humidity. Formulations containing stabilizers of the present invention stored under these conditions retain at least 80% of the bupropion hydrochloride in the composition at the time of storage. In many instance formulations of the present invention retain at least 85% and ideally retain at least 90% of bupropion hydrochloride in the composition
10 at the time of storage. Standard procedures such as HPLC may be used to determine the amount of active ingredient remaining after storage.

The aqueous solution pH of the stabilizers of this invention is determined by adding 15.7 grams of stabilizer to 5084 grams of deionized water in a Pyrex® beaker. The resulting mixture is stirred for approximately 15 minutes, using a stir plate and a
15 magnetic stir bar. The resulting solution is examined using a Corning® pH Meter Model 355. Solutions are stirred with a magnetic stir bar during analysis. Measurements are performed in duplicate and the average thereof is used.

Stabilizers of the present invention include inorganic acids meeting the aforementioned criteria and more specifically include but are not limited to hydrochloric
20 acid, phosphoric acid, nitric acid, and sulfuric acid, or combinations thereof. Hydrochloric acid is a preferred stabilizer.

Pharmaceutical compositions of the present invention may optionally include any conventional ingredients for improving the physical properties, visual appearance or odor of the pharmaceutical. Examples include, but are not limited to, lubricants such
25 as talc; binders such as starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone; diluents such as microcrystalline cellulose and lactose; disintegrants such as sodium starch glycolate, croscopovidone and croscarmellose sodium; and colorants.

The total amount of inactive ingredient in the formulation, including the amount
30 of stabilizer, is preferably more than 50% of the weight of bupropion hydrochloride in the composition and less than 650% of the weight of bupropion hydrochloride, i.e the ratio of inactive ingredient in the formulation, including the amount of stabilizer, to bupropion hydrochloride in the composition is between about 1:2 and about 6.5:1.

The amount of stabilizer may be from about 0.01% to 5% of the weight of
35 bupropion hydrochloride, i.e the ratio of stabilizer to bupropion hydrochloride in the composition is between about 1:10,000 to about 1:20. Ideally the amount of stabilizer

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is about 0.1% to about 2% of the weight of bupropion hydrochloride in the composition, i.e the ratio of stabilizer to bupropion hydrochloride in the composition is between about 1:1000 to about 1:50.

5 The suitable amount of stabilizer is based on the label strength of bupropion hydrochloride in the pharmaceutical formulation in solid dosage form and can be determined by one skilled in the art.

10 Pharmaceutical compositions of the present invention generally contain 25 mg to 500 mg of bupropion hydrochloride. More preferred compositions of the invention contain 50 mg, 75 mg, 100 mg or 150 mg of active ingredient and may be in the form of tablets, caplets or capsules. Immediate, modified, or extended release profiles, or combinations thereof, are encompassed by the present invention.

15 Pharmaceutical compositions of the present invention are prepared by preparing a dilute solution of inorganic acid and adding the dilute inorganic acid solution to a dry blend of bupropion hydrochloride and other active and inactive ingredients. The mixture is granulated, dried and milled. Solid dosage formulations are prepared such as by compressing the milled granulation to form tablets or caplets. Alternatively, capsules may be prepared by placing the milled granulation in, for example, a two-part hard gelatin capsule.

20 Solid dosage forms such as the aforementioned may optionally be film coated using an aqueous coating solution or suspension which has been acidified to a pH of about 0.5 to about 4.0. In preferred embodiments of the invention, the aqueous coating solution or suspension is acidified using a dilute inorganic acid such as hydrochloric acid, phosphoric acid, nitric acid, and sulfuric acid to provide an acidic environment on the tablet surface, thereby providing improved stability and further minimizing degradation of bupropion hydrochloride. Dilute, as used herein refers to about 25 0.095 N to about 0.105 N and preferably 0.1 N.

Suitable coating solutions are commercially available and known to those skilled in the art. Coating agents are also described in Handbook of Pharmaceutical Excipients, (Wade and Weller, ed., 2nd ed.)

30 The following examples are illustrative, but are not limiting of the present invention. Throughout the examples, NF and USP are designations for standards published in the National Formulary and U.S. Pharmacopoeia, respectively.

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Example 1

The formulation contained the following ingredients in the following amounts:

5	Ingredient	Weight per Tablet (mg) 75 mg potency
	Bupropion Hydrochloride	75.0
	Cellulose, Microcrystalline, NF	332.0
	Talc, USP	23.0
10	Hydroxypropyl Cellulose, NF	10.0
	0.1 N Hydrochloric Acid	(0.113 mL)
	TOTAL	440.0

15

The ingredients were measured for a 45,000 tablet batch size.
The following ingredients were sifted through a #20 mesh screen:
Cellulose, Microcrystalline, NF
Bupropion Hydrochloride

20

Hydroxypropyl Cellulose, NF

The screened ingredients were transferred to a Collette Gral and mixed for ten (10) minutes, with choppers on for two (2) minutes. The mixed material was granulated with 0.1 N Hydrochloric Acid for a granulation time of twelve (12) minutes.

25

The granulated material was dried in the tray oven at 40 degrees C to a moisture Loss on Drying (LOD) of 1.5 - 3.5 % w/w. The moisture was measured using a Computrac® moisture analyzer. The granulated, dried material was milled through a model D-6 Fitzmill equipped with a #1 plate, knives forward, at medium speed.

30

Talc, USP was sifted through a #30 mesh screen into the milled material. The screened and milled material was blended in a Gemco Double Cone Blender for ten (10) minutes. The blended material was compressed on a Kikusui Libra tablet compression machine at a compression weight of about 0.440 grams per tablet.

The compressed tablet cores (22,727) were aqueous film coated using 2833 g of the following coating formulation:

35

Opadry White YS-1-7003	600 g
Purified Water, USP	3400 g
TOTAL:	4000 g

40

- 5 -

The purified water was added to a stainless steel container. To the same container Opadry White was slowly added. The resulting suspension was stirred using a stir bar until uniform and smooth. The tablet cores were coated using a Hi-Coater® 60 tablet coating machine.

- 5 Bed Temperature: 38° - 40°C
Inlet Temperature 70° C
Pan Speed during warming: 1 - 2 RPM
Pan Speed during coating: 10 - 11 RPM
Spray Rate: 48 g/min. - 53 g/min.

10

Product stability data were obtained for this formulation stored for 4 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 1.

15 **Table 1**

	Weeks	Potency (%)
	0	100.2
20	4	88.5

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Example 2

45,000 tablet cores were prepared as described in Example 1 except that the granulated material was dried in the fluid bed dryer in two parts.

The tablet cores were coated as follows:

The formulation for the acidified coating contained the following ingredients in the following amounts:

10	Ingredient	Quantity per Tablet
	Opadry White	18.7 mg
15	0.1 N Hydrochloric Acid	0.15 mL

The coating was prepared as follows:

Opadry White and 0.1N hydrochloric acid were mixed in a stainless steel container for approximately 30 minutes. The tablet cores were coated according to method of Example 1 using the acidified coating suspension. Product stability data were obtained for this formulation stored for 12 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 2.

Bupropion Hydrochloride - Assay

Table 2

	Weeks	Potency (%)
30	0	98.5
	4	99.0
	8	98.4
	12	96.4

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Example 3

5 The formulation contained the following ingredients in the following amounts:

	Ingredient	Weight per Tablet (mg) 75 mg potency
	Bupropion Hydrochloride	75.0
	Cellulose, Microcrystalline, NF	332.0
10	Talc, USP	23.0
	Hydroxypropyl Cellulose, NF	10.0
	Crospovidone	25.0
15	0.1 N Hydrochloric Acid	(0.118 mL)
	TOTAL	465.0

The ingredients were measured for a 45,000 tablet batch size.

The following ingredients were sifted through a #20 mesh screen:

- 20 Cellulose, Microcrystalline, NF
Bupropion Hydrochloride
Hydroxypropyl Cellulose, NF
Crospovidone (64% of total amount)

25 The screened ingredients were transferred to a 75 liter Collette Gral and blended for ten (10) minutes, with choppers on for two (2) minutes. The blended material was granulated with Hydrochloric Acid for a granulation time of eight (8) minutes.

The granulated material was dried in the fluid bed dryer in two parts to a moisture LOD of 1.5 - 3.5 % w/w. The moisture was measured using a Computrac® moisture analyzer.

30 The granulated, dried material was milled through a model D-6 Fitzmill equipped with a #1 plate, knives forward, at medium speed.

The milled material was blended in a 2 cu.ft. Gemco Double Cone Blender for ten (10) minutes.

35 The remaining Crospovidone was sifted through a #20 mesh screen into the milled material. The screened and milled material was blended in the Gemco Double Cone Blender for five (5) minutes. Thereafter, talc, USP was sifted through a #30 mesh screen into the blended material. The screened and milled material was blended in the Gemco Double Cone Blender for ten (10) minutes. The blended material was compressed on a Kikusui Libra tablet compression machine at a compression weight of
40 about 0.465 grams per tablet.

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The compressed tablet cores were aqueous film coated using the following coating formulation:

	Ingredient	Quantity per Tablet
	Opadry White YS-1-7003	18.7 mg
5	0.1 N Hydrochloric Acid Solution	0.15 mL

The coating suspension was prepared as follows:

The 0.1N Hydrochloric Acid solution was added to a container. To the same container, Opadry White was slowly added. The resulting suspension was stirred using a stir bar until uniform and smooth.

The tablet cores were coated according to the procedure described in Example 1 using a Hi-Coater® 60 tablet coating machine.

Tablet cores were coated to an approximate weight of 0.480 grams.

Product stability data were obtained for this formulation stored for 12 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 3.

Table 3

	Weeks	Potency (%)
25	0	97.6
	4	99.5
	8	98.8
	12	97.2

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Example 4

The formulation contained the following ingredients in the following amounts:

5	Ingredient	Weight per Tablet (mg)
		100 mg potency
	Bupropion Hydrochloride	100.0
	Cellulose, Microcrystalline, NF	442.7
	Talc, USP	30.7
10	Hydroxypropyl Cellulose, NF	13.3
	Crospovidone	33.3
	0.1N Hydrochloric Acid	(0.083 mL)
15	TOTAL	620.0

The ingredients were measured for a 42,000 tablet batch size.

The following ingredients were ~~added~~ through a #20 mesh screen:

- 20 Cellulose, Microcrystalline, NF (50% of total)
 Bupropion Hydrochloride
 Hydroxypropyl Cellulose, NF
 Crospovidone (64% of total)

- 25 The screened ingredients were transferred to a Collette Gral and blended for ten (10) minutes, with choppers on for two (2) minutes.

The blended material was granulated with Hydrochloric Acid for a granulation time of approximately 5 - 6 minutes.

The granulated material was dried in the fluid bed dryer to a moisture LOD of 1.5 - 3.5 % w/w.

- 30 The moisture was measured using a Computrac® moisture analyzer.

The granulated, dried material was milled through a model D-6 Fitzmill equipped with a #1 plate, knives forward, at medium speed.

- 35 The remaining cellulose microcrystalline, NF and crospovidone were screened through a #20 mesh screen. The screened and milled material was blended in a Gemco Double Cone Blender for ten (10) minutes.

The talc, USP was screened through a #30 mesh screen:

The screened and milled materials were blended in a Gemco Double Cone Blender for ten (10) minutes.

- 40 The blended material was compressed on a Kikusui Libra tablet compression machine at a compression weight of about 0.620 grams per tablet.

- 10 -

Product stability data were obtained for tablet cores prepared according to this formulation stored for 12 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 4.

5 **Table 4**

	Weeks	Potency (%)
	0	99.1
10	4	99.7
	8	97.2
	12	98.8

Example 5

15

The formulation was prepared as described in Example 4 using 100 mg of bupropion hydrochloride per tablet core. The granulated material was dried to a moisture LOD of 1.5 - 3.5 % w/w. The blended material was compressed on a Kikusui Libra tablet compression machine at a compression weight of about 0.620 grams per tablet.

20 Tablet cores were coated according to the procedure listed in Example 2 using Chromatone® P instead of Opadry White.

The formulation for the acidified coating contained the following ingredients in the following amounts:

25

	Ingredient	Quantity per Tablet
	Polyethylene Glycol, NF	1.6 mg
	Polysorbate 80, NF	0.2 mg
30	Chromatone® P DDB 8440-OR	17.9 mg
	0.1N Hydrochloric Acid	(0.11 mL)

35 The coating was prepared as follows:

The 0.1N hydrochloric acid was transferred to a stainless steel container with a mixer. Polysorbate 80, NF, Polyethylene glycol, NF and Chromatone® P DDB 8440-OR were added to the container. The resulting acidified coating suspension was stirred during this Step and for approximately 30 minutes before use. The tablet cores were

40 coated according to method of Example 1 using the acidified coating suspension.

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Product stability data were obtained for this formulation stored for 4 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 5.

5 **Table 5**

	Weeks	Potency (%)
	0	97.5
10	4	99.6

Example 6

15 The formulation contained the following ingredients in the following amounts:

	Ingredient	Weight per Tablet (mg) 100 mg potency
	Bupropion Hydrochloride	100.0
20	Cellulose, Microcrystalline, NF	420.2
	Talc, USP	30.7
	Hydroxypropyl Cellulose, NF	13.3
	Crospovidone, NF	55.8
25	0.1 N Hydrochloric Acid	(0.083 mL)
	TOTAL	620.0

30 The ingredients were measured for a 42,000 tablet batch size.

The following ingredients were sifted through a #20 mesh screen:

35 Cellulose, Microcrystalline, NF (50% of total)
Bupropion Hydrochloride
Hydroxypropyl Cellulose, NF
Crospovidone, NF (55% of total)

40 The screened ingredients were transferred to a Collette Gral and blended for ten (10) minutes, with choppers on for two (2) minutes. The blended material was granulated with Hydrochloric Acid for a granulation time of approximately 5 - 6 minutes.

The granulated material was dried in two parts in the fluid bed dryer to a moisture LOD of 1.5 - 3.5 % w/w.

45 The moisture was measured using a Computrac® moisture analyzer.

The granulated, dried material was milled through a model D-6 Fitzmill equipped with a #0 plate, knives forward, at medium speed.

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The remaining cellulose microcrystalline, NF and crospovidone were screened through a #20 mesh screen.

The screened and milled material was blended in a Gemco Double Cone Blender for ten (10) minutes. Thereafter the talc, USP was screened through a #30 mesh
5 screen. The screened and milled material was blended in a Gemco Double Cone Blender for ten (10) minutes.

The blended material was compressed on a Kikusui Libra tablet compression machine at a compression weight of about 0.620 grams per tablet.

Tablet cores were coated according to the procedure described in Example 5.

10 Product stability data were obtained for this formulation stored for 8 weeks at 40°C, 75% relative humidity. Potency was determined using HPLC. Product stability data are presented in Table 6.

Table 6

15	Weeks	Potency (%)
	0	96.7
	4	97.6
20	8	95.3

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CLAIMSWhat is claimed is:

1. A pharmaceutical composition in solid form comprising bupropion
5 hydrochloride and a pharmaceutically acceptable stabilizer in an effective stabilizing amount wherein said stabilizer is an inorganic acid.
2. The composition of claim 1 wherein said stabilizer forms an aqueous solution
having a pH of about 0.5 to about 4.0 at a concentration of about 0.31% w/w.
10
3. The composition of claim 1 wherein the stabilizer is hydrochloric acid,
phosphoric acid, nitric acid or sulfuric acid.
4. The composition of claim 3 wherein the stabilizer is hydrochloric acid.
15
5. The composition of claim 1 wherein the amount of stabilizer in the composition
is from about 0.01% to about 5.0 % of the amount of bupropion hydrochloride in the
composition.
- 20 6. The composition of claim 5 wherein the composition comprises from about 50
mg to about 300 mg of bupropion hydrochloride.
7. The composition of claim 1 further comprising a film coating wherein said film
coating is acidified to a pH of from about 0.5 to about 4.0.
25
8. The composition of claim 7 wherein said film coating is acidified using an
inorganic acid.
9. The composition of claim 8 wherein the inorganic acid is hydrochloric acid,
30 phosphoric acid, nitric acid or sulfuric acid.
10. The composition of claim 9 wherein the inorganic acid is hydrochloric acid.

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11. A method for stabilizing bupropion hydrochloride in solid form comprising
mixing a pharmaceutically effective amount of bupropion hydrochloride with an
effective stabilizing amount of a stabilizer wherein said stabilizer is an inorganic acid
5 which forms an aqueous solution having a pH of about 0.5 to about 4.0 at a
concentration of about 0.31% w/w.
12. The method of claim 11 wherein the stabilizer is hydrochloric acid, phosphoric
acid, nitric acid or sulfuric acid.
- 10 13. The method of claim 12 wherein the stabilizer is hydrochloric acid.
14. The method of claim 11 further comprising coating the tablet core with an
15 acidified film coating solution or suspension having a pH in the range of about 0.5 to
about 4.0.
15. The method of claim 14 wherein the film coating is acidified using an inorganic
acid.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/135 A61K9/20 A61K9/48 A61K47/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 03791 A (WELLCOME FOUND :SUTTON JOEL ELMORE JR (US); KALIDINDI SANYASI RAJU) 9 February 1995 see page 1, paragraph 4 see page 2 see page 4, paragraph 6 ---	1-15
Y	US 5 358 970 A (RUFF MICHAEL D ET AL) 25 October 1994 cited in the application see column 1 - column 2 -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9503791	A	09-02-1995	AU 698883 B	12-11-1998
			AU 7235294 A	28-02-1995
			CA 2168364 A	09-02-1995
			EP 0711154 A	15-05-1996
			HU 73677 A	30-09-1996
			JP 9506070 T	17-06-1997
			NO 960373 A	29-01-1996
			NZ 268951 A	24-03-1997
			SG 49790 A	15-06-1998
			US 5541231 A	30-07-1996
			US 5731000 A	24-03-1998
			US 5763493 A	09-06-1998
			ZA 9405668 A	29-01-1996
US 5358970	A	25-10-1994	US 5541231 A	30-07-1996
			US 5763493 A	09-06-1998